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Scientific Research

The effect of curcumin-loaded exosomes on the proliferation of human ovarian cancer SKOV3 cells

Reihaneh Ramezani[1, *], Hanieh Minatour Sajadi[2], Sadegh Babashah[3]

[1]Department of Family Therapy, Women Research Center, Alzahra University, Tehran, Iran
[2] Department of Biochemistry, Faculty of Life Sciences, Islamic Azad University, Tehran North Branch, Tehran, Iran
[3]Department of Genetics, Faculty of Sciences, Tarbiat Modares University, Tehran, Iran

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*Corresponding Author E-Mail:

re.ramezani@alzahra.ac.ir

ABSTRACT

Background: Curcumin is a polyphenol compound with many therapeutic effects. Despite the anti-tumor, antioxidant and anti-inflammatory properties of this pigment, due to poor solubility and instability in the aqueous environments and physiological conditions of the body, its application in the treatment of diseases has been limited. Today researchers are trying to design an efficient nanocarrier for employing this pigment in pharmaceutical applications. Exosomes are lipid nanovesicles are released into the extracellular environment by all types of cells and are responsible for the transfer of biological materials between cells, so they are considered the best candidate for this goal. In this study, we aimed to load curcumin into the exosomes to increase its solubility and stability and facilitate its delivery into ovarian cancer cells.
Methods: After isolating the exosome by ultracentrifugation and verifying its structure with SEM, TEM and DLS, curcumin was loaded into the exosome by three methods of incubation, sonication and freeze-thaw cycles. Then, using MTT assay, the toxicity effect of curcumin on SKOV3 cells was investigated.
Results: The results showed that the amount of curcumin loading into exosome was very low (less than 10%) and it was found that sonication and freeze-thaw cycles have no effect on increasing the loading of curcumin into the exosome. Based on the results of the toxicity test, IC50 value of free curcumin and exosome-loaded curcumin was 150 µg/ml and 200 µg/ml, respectively. Although the loading percentage of curcumin in the exosome was very low, the MTT results showed that the loading of curcumin in the exosome plays a significant role in its efficient delivery to SKOV3 cells.
Conclusions: It can be concluded that despite the very high stability of exosomes and the safety of these cellular nanovesicles, for better efficiency in drug delivery, more studies should be done for optimizing the methods of drug loading into exosomes.

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1. Introduction

Curcumin is a hydrophobic polyphenol compound and the active component of turmeric, derived from the root of *Curcuma longa*, a plant that grows in tropical or subtropical regions of Asia, including India and China [1]. Curcumin is a disinfectant and anti-inflammatory agent and has effective role in healing wounds. It is a versatile molecule with various therapeutic effects, as it interacts directly and indirectly with different biomolecules [1, 2] and inhibits their regulating functions. Thus, more than 30 different proteins directly interact with curcumin [3].

The effects of curcumin on angiogenesis, apoptosis, metastasis, cell cycle and its anticancer and therapeutic properties in breast cancer has been well-documented [4]. Curcumin has also been found to delay the progression of ovarian cancer, increase the sensitivity of these cancer cells to chemotherapy, and reduce the side effects of drugs used in ovarian cancer treatment [2].

Despite its wide range of biological and therapeutic effects, the use of curcumin as a therapeutic agent faces limitations. Due to its hydrophobicity, low solubility and bioavailability, curcumin cannot show the expected therapeutic effects [5, 6]. It is insoluble in water, but is easily dissolved in solvents such as ethanol, acetone, methanol, acetonitrile, chloroform and ethyl acetate [7, 8]. Curcumin is easily degraded in aqueous system, although its degradation rate decreases in solvents such as isopropanol, DMSO, and ethanol, depending on the concentration of the solvents [9]. However, since most of these solvents are toxic to cells, they cannot be used in high concentration to dissolve curcumin. Therefore, it is necessary to load curcumin in a safe and efficient nanocarrier to increase its solubility and stability as well as its cellular bioavailability [10]. Exosome is considered one of the best biological nanocarriers due to its unique features, including the transfer of various biomolecules such as proteins, miRNA and DNA from one cell to another. These small spherical nanoparticles arranging in size from 30 to 150 nm, are produced by all living cells and can be found in all biological fluids of the body including blood, tears, saliva, urine, breast milk, cerebrospinal fluid (CSF), semen, synovial fluid [11]. Therefore, the objective of this research is to increase the solubility and penetration of curcumin into ovarian cancer cells by its loading it into the exosome.

2.Methods

Cell culture

SKOV3 cell line was purchased from the Stem Cell Research Center (STRC, Tehran, Iran). These cells were cultured in DMEM medium (Gibco; Thermo Fisher Scientific, Inc.) supplemented with 10% fetal calf serum, FBS (Gibco; Thermo Fisher Scientific, Inc.), 2 mM L-glutamine, 100 units/ml penicillin, and 100 µg/ml streptomycin. These cells were incubated in a humidified incubator with 5% CO_2 at a temperature of 37 $^{\circ C}$.

Exosome purification

SKOV3 ovarian cancer cells were cultured until they reached 90% density. The cell culture medium was collected, and exosomes were isolated. To remove dead cells, the supernatant was first centrifuged at 1000× g for 10 minutes. Next, the centrifugation was performed at 9000× g for 30 minutes to remove cell debris. The resulting supernatant was then subjected to a high-speed centrifugation (Vision Scientific, Korea) at 100,000× g for 1 hour at a temperature of 4°C, and the obtained pellet was dissolved in PBS buffer and subsequently filtered.

Exosom charactерization

Dynamic light scattering (DLS)

The size distribution of exosomes was measured by Dynamic light scattering (DLS). Purified exosome samples diluted in PBS (1:100), and then the size of exosomes was measured by SZ-100 Nanoparticle Size Analyzer (HORIBA Scientific, Japan).

Transmission Electron Microscopy (TEM)

To prepare the sample for TEM imaging, negative staining was done. First, a 5 µl drop of exosome was placed on a formvar carbon-coated copper grid and placed at room temperature for a few minutes, and then the sample was slightly spread with a filter paper to form a thin layer of exosome suspension on the grid. Then 4% uranyl acetate (Merck, Darmstadt, Germany) was added and the grid was not shaken until it was completely dry. After preparing the samples, images were taken

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using a transmission electron microscope (Zeiss-EM10C).

Scanning Electron Microscopy (SEM)

Exosome solution was directly dropped onto a poly-L-lysine coated glass slide and air dried, then was fixed with 1 ml of 2.5% glutaraldehyde (Merck, Darmstadt, Germany) in 0.1 M sodium cacodylate solution, pH: 7, (Sigma-Aldrich) for 1 hour at 4°C. The sample was washed with 1 ml of 1.0 M sodium cacodylate buffer at room temperature. This step was repeated 3 times and each time for 10 minutes. Next, it was fixed with 1 ml of 2% osmium tetroxide for 1 hour at 4°C and it was washed with 0.1 M sodium cacodylate buffer. Then, it was incubated for 10 minutes by ethanol with different concentrations (50, 60, 70, 80, 90, 95 and 100%, respectively) on a shaker. Finally, in order to evaporate ethanol, it was incubated for 30 minutes at room temperature, and then imaging with a scanning electron microscope SEM (VEGA3, TESCAN, Czech Republic) was done.

Curcumin loading into exosomes

Curcumin was loaded into exosomes following three different loading methods: incubation, sonication, and freeze-thaw cycling.

Cur-Exo solution preparation:

First, curcumin was completely dissolved in ethanol. Then the concentration of ethanol was decreased to 50% by adding PBS (Ethanol: PBS, 1:1). Finally, the exosome with a concentration of 150 µg/ml was added to prepare Cur-Exo solution until the final ethanol concentration reached 1%.

Loading Methods:

For the incubation method, the Cur-Exo solution was kept for 1 hour at 37°C in the dark. The sonication method consisted of 6 cycles of 30 seconds was performed in a sonicator. A cooling time of 2 minutes was applied between each cycle due to protecting of exosomes membrane during sonication. In all the steps of sonication, the Cur-Exo solution was placed in an ice container. For the freeze-thaw cycling method, the Cur-Exo solution was alternatively frozen at -70 ºC and then thawed at room temperature. Sufficient care was taken to do freezing and thawing cycles without interruption as much as possible. The thermal shock was necessary to destabilize the exosome membrane.

Loading efficiency

To separate free curcumin from loaded curcumin (ExoCur), the Cur-Exo solution was centrifuged at 60,000×g for 2 hours and the supernatant was separated from the exosome pellet. The concentration of curcumin in the supernatant as an unloaded (free) curcumin was measured by Cecil CE2501 UV-visible spectrophotometer. Absorbance of the curcumin was measured at λmax=420 nm against blank. By placing this value in the following formula, the percentage of drug loading in the exosome was calculated. Finally, the purified exosomes were aliquoted and stored at −20 °C for further assays.

MTT assay

$$\text{Loaded Curcumin (\%)} = \frac{\text{primary curcumin concentration} - \text{unloaded curcumin concentration}}{\text{primary curcumin concentration}} \times 100$$

SKOV3 cells were seeded at a density of 8000 cells/well in a 96-well. After incubating the cells for 24 hours, four different concentrations of free curcumin (125, 250, 500 and 1000 µg/ml) were added to cells in triplicate. In order to evaluate the effect of curcumin-loaded exosomes (ExoCur) on SKOV3 cells, the concentrations of 20, 100 and 500 µg/ml of ExoCur were added to the cells. Then, the cells were incubated for 48 hours at 37°C and 5% CO2. The same concentration of exosomes alone was considered as the control, and DMEM was used as the blank sample. After overnight incubation, 10 µl of MTT solution was added to each well and incubated for 2 hours at 37 °C in 5% CO2. Next, the reaction was stopped by adding 100 µl of dimethyl sulfoxide (DMSO), the absorbance was measured at 570 nm after 10 minutes using an ELISA reader.

Statistical Analysis

All tests were performed as triplicates. Statistical studies were calculated using the two way ANOVA method. P value < 0.05 was considered as significant.

3.Results

Characterization of exosomes by electron microscopy imaging

To confirm the identity of the purified exosomes, their size and morphology were evaluated by SEM and TEM. Exosomes are typically stored in phosphate buffer (PBS) and as shown in figure 1-A, the SEM images did not

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have good quality due to the formation of salt crystals after drying of the samples. Since exosomes are bilayer lipid membrane, it was thought that creating suitable osmotic conditions on both its membrane sides is necessary for the stability of exosome structure, and replacing water instead of PBS buffer would not be possible. However, as seen in Figure 1-B, it was well established that exosomes are stable in water without salt. By omitting phosphate salt and replacing it with sterile water, the problem of forming salt crystals in exosome preparation for SEM imaging was completely solved (Fig.1).

The results of TEM also indicated the spherical nature of the isolated exosomes and their very good and high quantity (Fig. 1-C and D). Since phosphate salts are removed from the sample during the negative staining process before TEM imaging, the same problem as SEM was not present here.

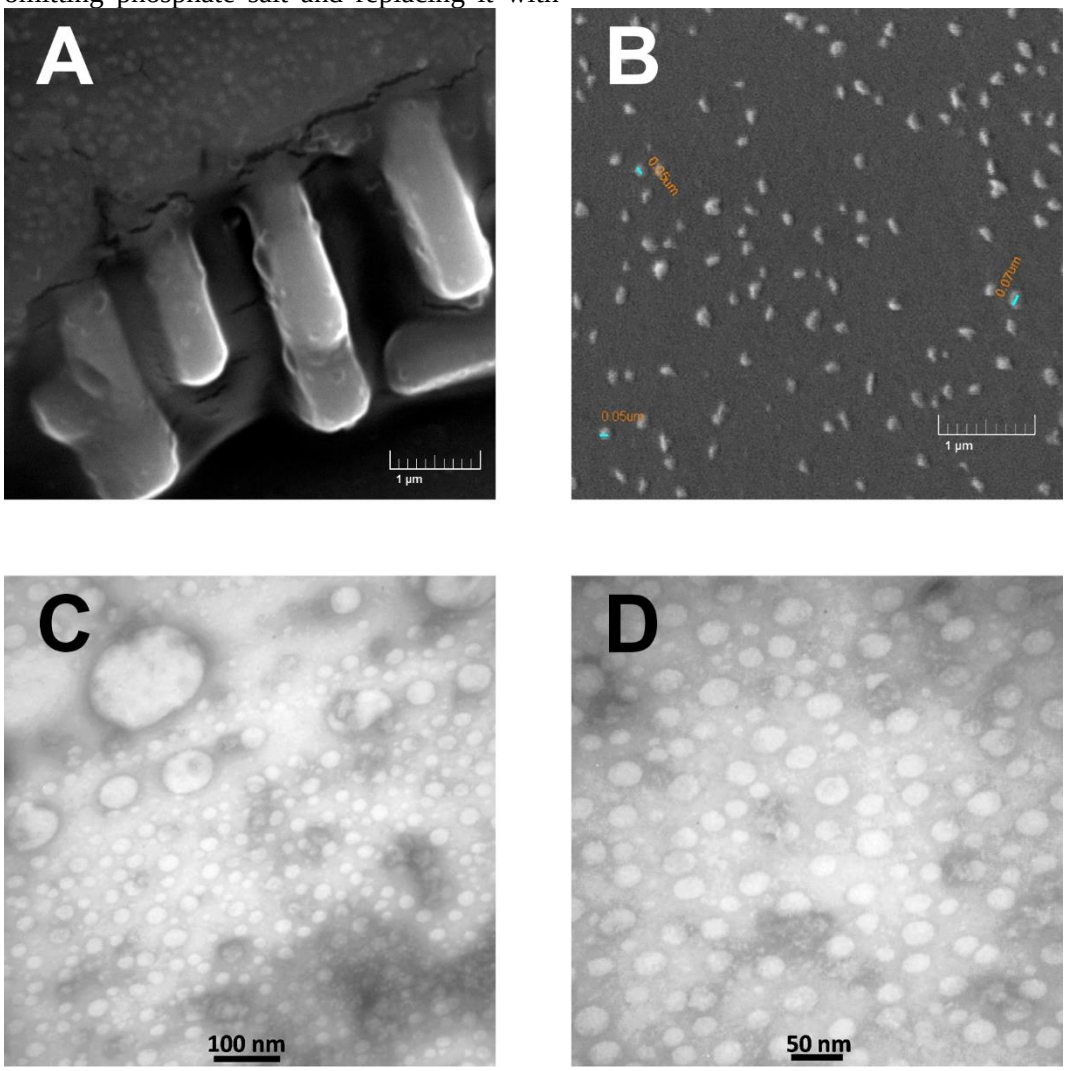

Figure 1. Characterization of exosomes by electron microscopy imaging. A, B: SEM images, C, D: TEM images. A, C and D: Exosomes were dissolved in PBS (pH; 7), B: Exosomes were dissolved in water.

Characterization of exosomes by Dynamic light scattering (DLS)

In DLS results, it was observed that most of the particles had a size of about 100 nm (Fig. 2). However, the TEM results showed that most of the particles had a size smaller than 50 nm and the number of particles with a size of 100 nm was very low. Since the DLS device is more sensitive to larger particles, it can be concluded that small particles were not detected by the DLS method in heterogeneous solution like exosomes. Therefore, the DLS method alone cannot be considered an accurate method for measuring the size of exosomes.

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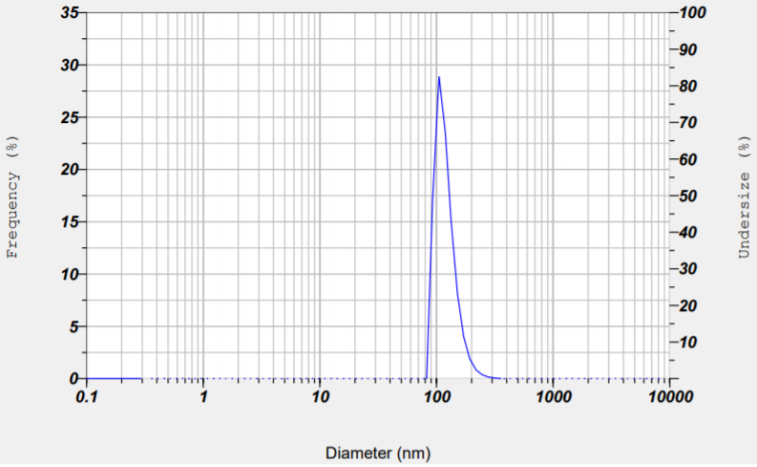

Figure 2. Particle size distribution by dynamic light scattering (DLS) of exosomes purified by ultracentrifugation.

Loading efficiency of curcumin in purified exosomes

To determine the amount of curcumin loading in the exosomes, UV-visible spectrophotometry was employed to measure the concentration of curcumin in the supernatant solution obtained from the ultracentrifugation of Cur-Exo solution. According to the obtained absorptions and the equation of the standard curve of curcumin, the average curcumin loading in exosomes was calculated as 10% for the incubation method, 11% for the sonication method, and 9% for the freeze-thaw cycling method.

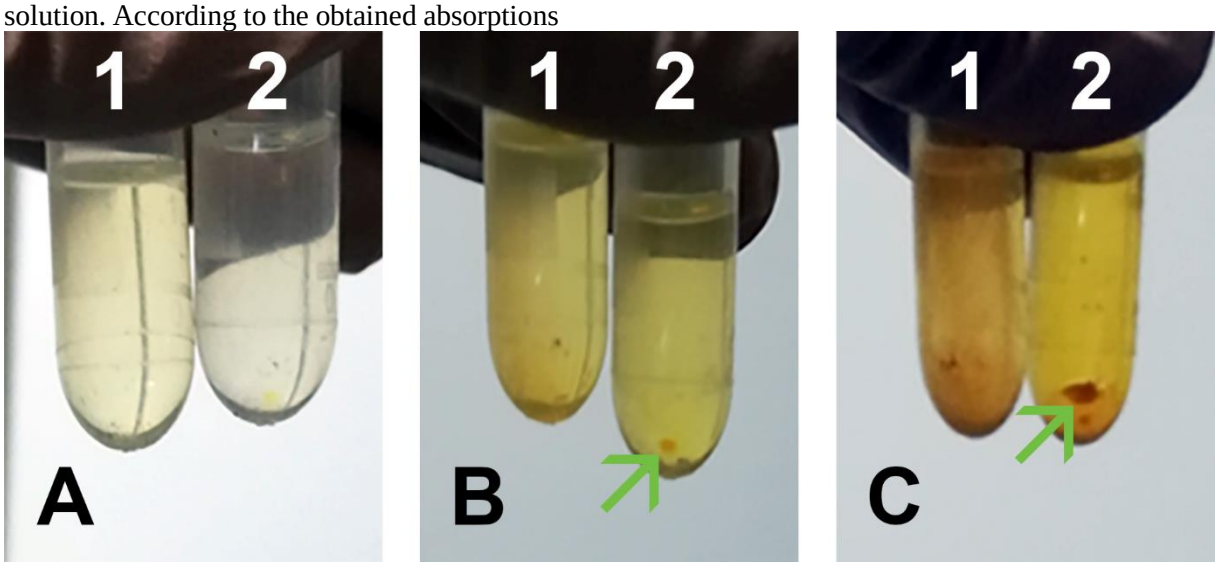

Figure 3. Observing the color of curcumin in exosome pellet after ultracentrifugation, concentration of A: 20 µg/ml, B: 100 µg/ml, C: 500 µg/ml of curcumin, loading method: incubation. The tubes number 1: without exososme (for checking), the tubes number 2: with exosome (Test tube). The arrows indicate the pellet of curcumin-loaded exosomes.

In vitro anti-tumor efficiency of the curcumin-loaded exosomes

To investigate the effect of curcumin on SKOV3 ovarian cancer cells, concentrations of 125, 250, 500 and 1000 µg/ml of free curcumin were used for treatment of cells. After 48 hours at the concentration of 125 µg/ml, a limited lethal effect was observed on the cells (Fig. 4-A). The toxicity of free curcumin at a concentration of 250 µg/ml on ovarian cancer cells was more than 50%, and at concentrations of 500 µg/ml and 1000 µg/ml, a significant number of cells died.

In the 48-hour treatment of ovarian cancer cells with curcumin loaded in exosomes (CurExo), the highest toxicity was observed at a concentration of 500 µg/ml of curcumin loaded in exosomes. (Fig 4-B.)

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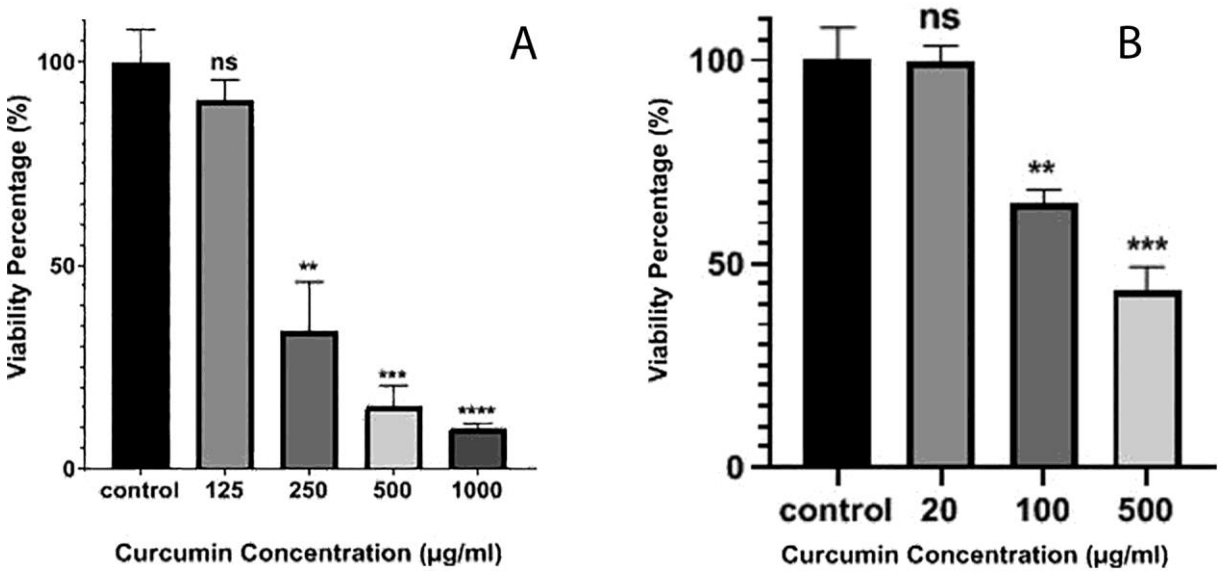

Figure 4. Cytotoxicity effect of free curcumin (A) and of curcumin-loaded exosomes (B) on SKOV3 cells.

4.Discussion

Curcumin is widely used in Asia, particularly India and China, as a traditional herb [12]. The anti-cancer and anti-inflammatory effect of curcumin has been well proven in various cancer cells [13-15]. A study showed that curcumin can cause apoptosis of SKOV3 ovarian cancer cells through the activation of Rho A/Rho-kinase signal pathway [16]. In another study, it was determined that curcumin exerts its anti-cancer effect on SKOV3 cells by modulating the PI3K/Akt-signalling pathway [17]. Additionally, curcumin can inhibit the proliferation of SKOV3 cells by increasing the expression of pro-apoptotic genes such as BAX, caspase-3 and caspase-9 and downregulating of BCL_2 [18]. Despite the anticancer properties, due to the very poor solubility of curcumin in aqueous and biological solutions and its instability, its application for therapeutic purposes has been limited [5]. The stability of the structure of curcumin is very low in water, PBS, plasma and serum-free cell culture medium, and it rapidly degrades when exposed to light [7, 19, 20]. Therefore, researchers are searching for an efficient nanocarrier to increase its solubility, stability and bioavailability. So far, various carriers have been studied for this purpose and satisfactory results have been obtained [10, 21-23]. Among these nanocarriers, exosomes have recently received special attention [24, 25]. Exosomes are produced by all cells and play a crucial role in the transportation of biological molecules and intercellular communication. Therefore, exosomes are considered one of the best candidates for loading curcumin and transferring it to the cell [26]. Numerous studies have have investigated the effects of curcumin-loaded exosomes on wound healing, cancer treatment, oxidative stress, brain disorders, cholesterol, and endothelial dysfunction with positive results [20, 27, 28]. Recent research has demonstrated that milk exosomes can be used for curcumin loading [29], and the results have indicated that milk exosomes easily enhance curcumin penetration into MDA-MB-231 and MCF-7 breast cancer cells and that the antiproliferative properties of curcumin loaded in bovine milk-derived exosomes have been well characterized [30, 31].

Ovarian cancer has remained the leading cause of death among women suffering from cancer [32]. Given the previous research on the anticancer effect of curcumin-loaded exosomes in other types of cancer [30, 33, 34], this study aimed to investigate the effect of curcumin-loaded exosomes on SKOV3 ovarian cancer cells. Three methods of incubation, sonication, and freeze-thaw cycles were utilized to load curcumin in exosomes. It was anticipated that ultrasonic waves and thermal shock would increase the loading percentage of curcumin in the exosomes by destabilizing and permeabilizing the exosome membrane. However, the results revealed that these methods did not significantly increase drug loading. This may be attributed to the high stability of the exosome membrane. Evaluation of the loading percentage demonstrated that only 10% of curcumin was successfully loaded into the exosomes, and increasing curcumin in

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the Cur-Exo solution did not have any effect on the loading amount. Despite of the low loading of curcumin, interestingly the curcumin loaded exosomes had a very indicative anti-proliferative effect on SKOV3 cells, and it confirmed that the exosome can increase the penetration of the curcumin into the cells.

5.Conclusion

Although exosomes have many advantages such as high stability and safety for delivery of drugs such as curcumin, but the low loading efficiency of drug in exosomes is as a major barrier to their translation to the clinic. Therefore suitable and high-efficiency loading methods must be identified for employing this very useful nanocarrier in therapeutic application.

List of abbreviations

SKOV3: human ovarian cancer cell line; SEM: Scanning Electron Microscopy; TEM: Transmission Electron Microscopy; DLS: Dynamic Light Scattering; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; IC50: Half maximal Inhibitory Concentration; DMSO: Dimethyl sulfoxide; CSF: cerebrospinal fluid; DMEM: Dulbecco's Modified Eagle's Medium; FBS: Fetal Bovine Serum; PBS: P Phosphate-buffered saline; BAX: BCL2 Associated X, Apoptosis Regulator; BCL2: B-cell lymphoma 2; MDA-MB-231: an epithelial human breast cancer cell line; MCF-7: human breast adenocarcinoma cell line.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available due to the request of the authors but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conception and manuscript design: RR. Collection of data: HMS. and RR. Manuscript writing: RR. Figure design: RR. Revision of the manuscript: RR and SB. All authors reviewed and approved the final version of the manuscript.

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ریحانه رمضانی[۱،*]، هانیه میناتور سجادی[۲]، صادق باباشاه[۳]

[۱] استادیار، گروه خانواده درمانی، پژوهشکده زنان، دانشگاه الزهرا، تهران، ایران

[۲] دانش‌آموخته کارشناسی ارشد، گروه بیوشیمی، دانشکده علوم زیستی، دانشگاه آزاد اسلامی واحد تهران شمال، تهران، ایران

[۳] دانشیار، گروه ژنتیک، دانشکده علوم پایه، دانشگاه تربیت مدرس، تهران، ایران

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* مسئول مکاتبات

re.ramezani@alzahra.ac.ir

چکیده

پس‌زمینه: کورکومین یک ترکیب پلی‌فنلی است که از ریزوم گیاه زردچوبه استخراج می‌شود. با وجود خواص ضد توموری، آنتی‌اکسیدانی و ضد التهابی این رنگدانه، به دلیل حلالیت ضعیف و ناپایداری در محیط‌های آبی و شرایط فیزیولوژیکی بدن، کاربرد آن در درمان بیماری‌ها محدود شده است. امروزه محققان در تلاشند تا یک نانوحامل کارآمد برای استفاده از این رنگدانه در کاربردهای دارویی طراحی کنند. اگزوزوم‌ها نانووزیکول‌های لیپیدی هستند که توسط انواع سلول‌ها در محیط خارج سلولی رها می‌شوند و وظیفه انتقال مواد بیولوژیکی بین سلول‌ها را بر عهده دارند، بنابراین بهترین انتخاب برای این هدف محسوب می‌شوند. در این مطالعه، بارگذاری کورکومین در اگزوزوم‌ها برای افزایش حلالیت و پایداری آن و تسهیل تحویل آن به سلول‌های تخمدانی مورد ارزیابی قرار گرفت.

روش‌ها: پس از جداسازی اگزوزوم با اولتراسانتریفیوژ و بررسی ساختار آن با DLS، SEM و TEM کورکومین با سه روش انکوباسیون، سونیکاسیون و چرخه‌های متوالی انجماد- ذوب در اگزوزوم بارگذاری و سپس با استفاده از روش MTT ، اثر سمیت کورکومین بر سلول‌های SKOV3 بررسی شد.

یافته‌ها: نتایج نشان داد که میزان بارگذاری کورکومین در اگزوزوم بسیار کم (کمتر از ۱۰ درصد) بوده و سونیکاسیون و اعمال چرخه‌های انجماد-ذوب هیچ تأثیری بر افزایش بارگذاری کورکومین در اگزوزوم‌ها ندارند. بر اساس نتایج تست سمیت، مقدار IC50 کورکومین آزاد و کورکومین بارگذاری شده به ترتیب ۱۵۰ و ۲۰۰ میکروگرم بر میلی لیتر بود. اگرچه درصد بارگذاری کورکومین بسیار پایین بود، اما نتایج سنجش MTT نشان داد که بارگذاری کورکومین در اگزوزوم نقش مهمی در تحویل کارآمد آن به سلول‌های SKOV3 دارد.

نتیجه‌گیری: می‌توان نتیجه گرفت که با وجود پایداری بسیار بالای اگزوزوم‌ها و ایمنی این نانووزیکول‌های سلولی، برای کارایی بهتر در دارورسانی، باید مطالعات بیشتری برای بهینه‌سازی روش‌های بارگذاری دارو در اگزوزوم‌ها انجام شود.

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